Effects of Huanglian Jiedu Decoction on Pain Behaviors in Rat Models of Postherpetic Neuralgia

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Abstract [**Objectives**] To observe the effects of Huanglian Jiedu Decoction on pain behaviors in rat models of postherpetic neuralgia (PHN) and analyze potential mechanisms. [**Methods**] Twenty SD rats with PHN models induced by intraplantar injection of 50 μL (6×10^6) varicella-zoster virus (VZV) into the left hind paw were randomly divided into two groups ($n = 10$ each) using a random number table: the model group (PHN group) and the Huanglian Jiedu Decoction group. From day 7 after inoculation, the Huanglian Jiedu Decoction group received oral gavage of Huanglian Jiedu Decoction twice daily for 14 days, while the PHN group received an equal volume of 0.9% saline. Thermal withdrawal latency (TWL) and mechanical withdrawal threshold (MWT) were measured at 1, 4, 7, 14, and 21 d after inoculation. Pain-related behaviors (vocalization, scratching, and licking/biting of the hind paw) were recorded. [**Results**] Compared with the PHN group, the Huanglian Jiedu Decoction group exhibited significantly prolonged TWL and increased MWT at days 14 and 21 ($P < 0.05$). At day 4 post-inoculation, both groups showed marked pain-related behaviors (*e.g.*, vocalization, scratching, licking/biting). These behaviors persisted until day 21 in the PHN group but significantly decreased in the Huanglian Jiedu Decoction group at days 14 and 21 ($P < 0.05$). [**Conclusions**] Huanglian Jiedu Decoction reduces pain sensitivity and alleviates pain-related behaviors in PHN model rats. The mechanism may involve elevating pain thresholds and decreasing pain conduction velocity.

Key words Huanglian Jiedu Decoction, Postherpetic neuralgia (PHN), Pain-related behaviors, Pain threshold

1 Introduction

Herpes zoster (HZ) is a cutaneous infectious disease characterized by skin blisters accompanied by severe pain, resulting from human infection with varicella-zoster virus (VZV)[1]. As a herpesvirus highly susceptible to humans, VZV exhibits neurotropism. Following initial infection presenting as chickenpox, the virus may remain latent in neural axis structures such as dorsal root ganglia and cranial nerve ganglia in some HZ patients after chickenpox resolution, causing severe neuropathic pain[2]. When immunity declines during spring and autumn seasons, the latent VZV reactivates and proliferates rapidly. The reactivated virus travels along sensory nerve fibers to the corresponding dermatomes, inducing intense cutaneous pain known as postherpetic neuralgia (PHN)[3]. Thus, targeting VZV is crucial for preventing neuropathic pain. Accordingly, this experiment administered Huanglian Jiedu Decoction to PHN model rats via gavage to observe its effects on pain-related behaviors and analyze potential underlying mechanisms.

2 Materials and methods

2.1 Animals Twenty SPF-grade Sprague-Dawley (SD) rats, aged 8 weeks and weighing 200 - 260 g (sex unspecified), were purchased from the Hubei Provincial Laboratory Animal Center [Certification No.: SCXK (E) 2019-0005]. The animals were housed and all experiments were conducted at the Animal Experiment Center of Taihe Hospital in Shiyan City, Hubei Province.

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2.2 Reagents and equipment CV-1 cells (African green monkey kidney fibroblasts) and VZV were purchased from Nanjing KeyGen Biotech Co., Ltd. The plantar thermal radiation algesiometer was procured from Shanghai Rui Bao Biological Technology Co., Ltd. Huanglian Jiedu Decoction was sourced from the Traditional Chinese Medicine Dispensary of Taihe Hospital in Shiyan, Hubei Province.

2.3 Rat PHN modeling and grouping CV-1 cells were cultured in DMEM/F12 complete medium to prepare a cell suspension, which was transferred to culture flasks at $5 \times 10^4/cm^2$ density, followed by VZV inoculation; approximately 2 d after inoculation, 80% of CV-1 cells showed infection, at which point infected cells were collected using phosphate-buffered saline (PBS) to prepare the VZV inoculum solution (containing $\approx 6 \times 10^6$ infected cells). Subsequently, twenty weight-matched rats were anesthetized with diethyl ether, and 50 μL of the VZV inoculum was injected into the left interdigital web to establish PHN models. Finally, all rats were randomly divided into two equal-sized groups ($n = 10$ each) using a random number table: the PHN group and the Huanglian Jiedu Decoction group.

2.4 Treatment Starting on day 7 post-inoculation, the Huanglian Jiedu Decoction group received 10% Huanglian Jiedu Decoction via gavage at 0.4 mL/100 g body weight twice daily (morning and evening) for 14 consecutive days (covering observation time points on days 14 and 21), while the PHN control group was administered an equal volume of 0.9% sodium chloride solution.

2.5 Behavioral observation At 1, 4, 7, 14, and 21 d after VZV inoculation, the frequencies of pain-related behaviors (vocalization, scratching, and licking/biting of the hind paws) were systematically recorded.

2.6 Determination of thermal withdrawal latency (TWL) and mechanical withdrawal threshold (MWT) At 1, 4, 7, 14, and 21 d after VZV inoculation, thermal withdrawal latency (TWL) was measured by irradiating hind paws using a plantar thermal radiation algesiometer (stimulus duration: 50 ms, pulse interval: 10 sec), recording the time (sec) from irradiation onset to paw withdrawal reflex, with the mean value calculated from 5 trials per rat; concurrently, mechanical withdrawal threshold (MWT) was assessed using an Electronic Von Frey algesiometer applied to bilateral hind paws, determining the minimal force (g) required to elicit paw lifting or licking behaviors, similarly averaging 5 trials per rat[4].

2.6 Statistical analysis Statistical analysis was performed using SPSS 26.0 software, with experimental data expressed as mean ± standard deviation ($\bar{x} \pm s$). Intra-group and inter-group comparisons were conducted using LSD pairwise *t*-tests, with $P < 0.05$ considered statistically significant.

3 Results and analysis

3.1 Behavior changes of rats As shown in Table 1, the PHN group exhibited behaviors such as vocalization, scratching, and licking/biting of the lower toes as early as 4 d after inoculation. These behaviors peaked on day 7 and persisted until day 21, with frequent occurrences. In the Huanglian Jiedu Decoction group, the frequency of these behaviors (vocalization, scratching, and licking/biting of the lower toes) was significantly lower compared to the PHN group on days 14 and 21. A statistically significant difference ($P < 0.05$) was observed between the Huanglian Jiedu Decoction group and the PHN group at these time points.

Table 1 Behavior changes of rats ($\bar{x} \pm s$, $n = 10$)

Inoculation days//d	Frequency of vocalizations		Times of scratching, and licking/biting of the lower toes	
	PNH group	Huanglian Jiedu Decoction group	PNH group	Huanglian Jiedu Decoction group
1	8.64 ± 0.33	8.14 ± 0.28	3.46 ± 0.11	2.89 ± 0.07
4	14.07 ± 0.88	13.43 ± 1.37	28.07 ± 0.84	28.50 ± 1.49
7	18.73 ± 1.49	18.00 ± 1.90	36.73 ± 2.50	36.81 ± 2.40
14	16.40 ± 1.32	10.15 ± 0.79a	34.49 ± 1.65	16.10 ± 0.25[a]
21	15.56 ± 1.48	3.42 ± 0.12a	33.20 ± 1.43	9.04 ± 0.45[a]

NOTE Compared with PNH group, [a]$P < 0.05$, the same below.

3.2 TWL and MWT results of rats As shown in Table 2, the Huanglian Jiedu Decoction group exhibited prolonged thermal withdrawal latency (TWL) and increased mechanical withdrawal threshold (MWT) on days 14 and 21. A statistically significant difference ($P < 0.05$) was observed compared to the PHN group at the same time points.

Table 2 TWL and MWT results of rats ($\bar{x} \pm s$, $n = 10$)

Inoculation days//d	PWL results//g		MWT results//s	
	PNH group	Huanglian Jiedu Decoction group	PNH group	Huanglian Jiedu Decoction group
1	14.37 ± 0.88	14.90 ± 0.99	5.70 ± 0.10	5.50 ± 0.08
4	5.57 ± 0.19	5.93 ± 0.17	9.74 ± 0.25	9.72 ± 1.20
7	2.66 ± 0.08	2.90 ± 0.32	17.40 ± 0.25	17.20 ± 0.79
14	4.66 ± 0.12	6.27 ± 0.19[a]	17.33 ± 0.81	12.56 ± 0.70[a]
21	6.93 ± 0.40	11.59 ± 0.43[a]	20.60 ± 1.70	7.01 ± 0.43[a]

4 Discussion

HZ, also known as snake-coiling sores, snake-string sores, waist-surrounding fire cinnabar, or waist-coiling dragon[5], is frequently complicated by persistent neuropathic pain after rash healing, called PHN[6]. Due to Varicella – Zoster Virus's (VZV) neurotropic and dermatotropic properties, reactivation occurs when host immunity declines. VZV invades dorsal root ganglia, triggering ganglionic inflammation that may progress to necrosis in severe cases. This experiment demonstrated that PHN-model rats exhibited pain-related behaviors including vocalizations, scratching, and licking/biting of lower toes as early as day 4 post-inoculation. These behaviors peaked on day 7 and persisted through day 21. Concurrently, the PHN group showed significantly shortened Thermal Withdrawal Latency (TWL) and decreased Mechanical Withdrawal Threshold (MWT) at all measured timepoints (days 4, 7, 14, and 21), indicating sustained neuropathic pain. In contrast, Huanglian Jiedu Decoction treatment resulted in prolonged TWL and elevated MWT on days 14 and 21. Neuropathic pain behaviors were concomitantly alleviated, with significantly reduced frequencies of vocalizations, scratching, and licking/biting. These findings suggest that Huanglian Jiedu Decoction modulates neuronal hyperexcitability at inflamed sites and attenuates hypersensitivity to mechanical stimuli.

In summary, Huanglian Jiedu Decoction reduces pain sensitivity and significantly alleviates pain-related behavioral changes in PHN model rats. The underlying mechanisms may involve enhancing viral clearance of VZV while concurrently attenuating neuronal hyperexcitability at inflammatory sites and diminishing hypersensitivity to mechanical stimuli, thereby alleviating neuropathic pain induced by inflammatory mediators.

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